Acute drug desensitization

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Introduction

Acute drug desensitization is the process by which a drug-allergic individual is converted from a highly sensitive state to a state in which the drug is tolerated. The procedure involves the cautious administration of incremental doses of the drug over a period of hours to days and it is used primarily in the management of IgE-mediated drug hypersensitivity reactions. More recently, this technique also has been used successfully in the management of other forms of immunopathology.

Acute desensitization may be considered in those patients in whom IgE antibodies to a particular drug are known or are presumed to exist and no alternative treatment agent is available. In addition, drug desensitization may be effective for other reactions that are delayed in onset, that appear to be immune in nature, but that are not IgE-mediated. While most of the desensitization protocols have involved betalactam antibiotics [1–4], this principle has been applied successfully to other agents as well [5–7] and they include: other antibiotics, insulin, chemotherapeutic agents, vaccines, heterologous sera and other proteins (Tables 1 and 2).

Mechanism(s) responsible for acute desensitization

In studies of patients who were shown to have penicillin-specific IgE antibodies and who underwent successful penicillin desensitization, the data suggest that antigen-specific, mast cell desensitization is responsible for the tolerant state [1,4,8]. Mediator depletion appears to play no role [5]. The fact that wheal-and-flare skin test responses to penicillin often become negative with successful desensitization, while IgE responses to other antigens remain unchanged, also supports the involvement of an antigen-specific mechanism [2,4,5]. Interestingly, both clinical reactivity and skin-test reactivity return within a few days unless a chronic tolerant state is maintained by continued drug administration. This finding indicates that the desensitized state is dependent upon the continuous presence of antigen and that clinical sensitivity returns rapidly in the absence of antigen.

The underlying mechanism responsible for the antigen-specific desensitized state remains unclear. Sullivan [5] hypothesizes that IgE receptor aggregation may generate counter-regulatory forces that, instead of causing cell activation, actually extinguishes activating signals. During desensitization, the drug is introduced slowly, and drug concentrations rise gradually. Thus, it is possible that slow rates of receptor aggregation caused by the gradual increase in drug concentration, along with suppression of cellular activation signals, may lead to antigen-specific desensitization and clinical tolerance. In addition, it is likely that during the desensitization process, univalent drug-haptenated proteins are formed and contribute to the desensitized state by inhibiting the cross-linking of drug-specific IgE molecules on mast cells. The finding that monovalent hapten can specifically inhibit allergic drug reactions [9,10] further supports a role for hapten inhibition in drug desensitization.

Desensitization procedure

Drug desensitization should be performed with the drug that is required for therapy and either the oral or intravenous route may be used. The starting dose for the procedure can be determined by performing intradermal skin tests with the native drug at a dose that does not cause a non-specific irritant reaction. For example, if a 0.02 mL intradermal injection of a drug at a 1 mg/mL concentration does not cause a local or systemic reaction, oral desensitization may be started at the dose injected (i.e. the tolerated dose, 20 μg).

Parenteral desensitization typically begins with 1/10 or 1/100 of the dose that was administered intradermally. Rapid desensitization protocols occur over several hours. Drug doses typically are doubled every 15 min and vital signs and peak flow values are monitored before and throughout the procedure. Mild complications of drug desensitization include pruritus or pruritic rashes and these complications may occur in up to one-third of the desensitizations performed. These reactions may require adjustments in dosing and/or intervals as well as the use of symptomatic medications. If more severe complications occur, such as bronchospasm or hypotension, the next dose should be reduced greater than 10-fold and repeated.
some instances, the desensitization procedure may have to be aborted.

It is critical that the individuals involved with the desensitization procedure (nurses, physicians, etc.) understand that this is a serious procedure. While anaphylactic reactions rarely occur if conservative protocols are used, health care personnel must be prepared to treat anaphylaxis if it does happen. It is also critical that both the patient and the healthcare personnel understand the importance of uninterrupted therapy after the procedure is completed since anaphylactic sensitivity, most likely, will return after the drug is withdrawn.

Summary

Evidence is accumulating that supports a role for acute desensitization for IgE-mediated drug allergy in those patients for whom no alternative drug exists. While most of the studies have been performed in penicillin-allergic patients, this procedure has been used safely in patients with IgE sensitivity to other agents. In addition, it has been shown that modified desensitization protocols may be effective in the prevention of other immune-mediated drug reactions, as well. Thus, while much research remains to be done in this area, drug desensitization will continue to be a powerful tool in the management of drug allergy.

References

1 Sullivan TJ. Antigen specific desensitization of patients allergic to penicillin J Allergy Clin Immunol 1982; 69: 500.

Table 1 Successful antibiotic desensitizations

| Penicillins | Cephalosporins |
| Sulphonamides | Vancomycin |
| Aminoglycosides | Pentamidine |
| Clindamycin | Anti-tubercular agents |

Table 2 Successful desensitizations to other agents

| Chemotherapeutics | Corticotropin |
| Insulin | Heparin |
| LHRH | Antivenoms |
| Measles vaccine | Heterologous sera |
| Tetanus toxoid | Deferoxamine |
| D-penicillamine | Carbamazepine |